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Comparison of Culture-Based and Molecular Methods for Diagnosis of Invasive Fungal Infections

Anjali Singh[1], Sashi Kant[2], Ramesh Yadav[3]

[1,2]Tutor, Department of Microbiology, Government Medical College, Jalun Orai, India

[3]Associate Professor, Department of Microbiology, Government Medical College, Jalun Orai, India

Abstract: ***Background***: Invasive fungal infections (IFIs) are a significant cause of morbidity and mortality in immunocompromised patients. Rapid and accurate diagnosis is crucial for effective management.

Objective: To compare the diagnostic performance of culture-based and molecular methods for detecting IFIs in high-risk patients.

Methods: This prospective study enrolled 500 immunocompromised patients with suspected IFIs. Clinical specimens (blood, bronchoalveolar lavage fluid, tissue biopsies, and cerebrospinal fluid) were analyzed using both conventional culture methods and PCR-based molecular assays. Diagnostic performance, turnaround time, and species distribution were evaluated.

Results: Molecular methods demonstrated higher sensitivity (91.2% vs 68.5%, $p<0.001$) and faster turnaround time (median 8 hours vs 72 hours, $p<0.001$) compared to culture-based techniques while maintaining high specificity (97.8% vs 99.1%, $p=0.08$). The overall agreement between methods was good (kappa = 0.78). Molecular techniques detected fungal pathogens in 10% of cases missed by culture. *Candida albicans* (39.5%) and *Aspergillus fumigatus* (20.9%) were the most frequently identified species.

Conclusions: Molecular methods offer superior sensitivity and rapid turnaround time for diagnosing IFIs compared to conventional culture techniques. These findings support the integration of molecular diagnostics into clinical algorithms for managing suspected IFIs in immunocompromised patients. However, the complementary roles of both methods should be recognized, and implementation should consider cost-effectiveness and the potential for detecting colonizing fungi.

Keywords: Aspergillus, Antifungal Therapy, Candida, Invasive Fungal Infections, Molecular

Corresponding Author:
Yadav Ramesh
Associate Professor,
Department of Microbiology,
GMC Jalaun, Orai, India.
Email ID: drramesh8726@gmail.com

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INTRODUCTION

Invasive fungal infections (IFIs) have emerged as a significant cause of morbidity and mortality, particularly among immunocompromised patients. These infections, caused by opportunistic fungi such as Candida, Aspergillus, and Cryptococcus species, pose a substantial challenge to clinicians due to their complex pathogenesis and the difficulties associated with their timely and accurate diagnosis (Serrano et al., 2003). The incidence of IFIs has risen dramatically over the past few decades, paralleling the increase in immunocompromised populations, including those with HIV/AIDS, hematological malignancies, solid

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organ transplants, and those receiving immunosuppressive therapies (Serrano et al., 2003).

The diagnosis of IFIs remains a critical bottleneck in patient management, as early and accurate identification of the causative fungal pathogen is crucial for initiating appropriate antifungal therapy and improving patient outcomes. Traditionally, culture-based methods have been the gold standard for fungal identification. These techniques involve the isolation and cultivation of fungi from clinical specimens, followed by morphological and biochemical characterization. While culture-based methods offer the advantage of isolating viable organisms for susceptibility testing, they are hampered by several limitations, including slow turnaround times, low sensitivity, and the inability to detect certain fastidious or slow-growing fungi (Arvanitis et al., 2014).

In recent years, molecular diagnostic methods have gained prominence as powerful tools for the rapid and sensitive detection of fungal pathogens. These techniques, primarily based on nucleic acid amplification and detection, offer several advantages over conventional culture-based methods. Molecular approaches, such as polymerase chain reaction (PCR), DNA sequencing, and more recently, next-generation sequencing (NGS), enable the direct detection of fungal DNA in clinical specimens, potentially reducing the time to diagnosis and improving sensitivity (Irinyi et al., 2016). Moreover, molecular methods can identify fungi to the species level with high accuracy, which is particularly important given the species-specific differences in antifungal susceptibility profiles. The development of panfungal PCR assays targeting conserved regions of the fungal genome, such as the internal transcribed spacer (ITS) region, has further expanded the utility of molecular diagnostics in detecting a broad range of fungal pathogens (Lackner et al., 2012). Additionally, multiplex PCR assays allow for the simultaneous detection of multiple fungal species, enhancing the efficiency of diagnostic workflows. Real-time PCR techniques have further improved the rapidity and quantitative capabilities of molecular diagnostics, enabling the monitoring of fungal burden and treatment response (White et al., 2015).

Despite these advantages, molecular methods are not without limitations. The high sensitivity of PCR-based techniques can lead to false-positive results due to environmental contamination or the detection of colonizing fungi. Furthermore, the presence of fungal DNA does not necessarily indicate active infection, necessitating careful interpretation of results in the clinical context. The standardization of molecular assays across laboratories and the lack of consensus on optimal DNA extraction methods and PCR protocols remain ongoing challenges in the field (Alanio et al., 2016). The comparison of culture-based and molecular methods for the diagnosis of IFIs has been the subject of numerous studies, with varying results depending on the specific techniques employed, the patient population studied, and the types of fungi investigated. Some studies have demonstrated superior sensitivity of molecular methods compared to culture, particularly in the context of invasive aspergillosis and candidemia (Arvanitis et al., 2015). Others have highlighted the complementary nature of these approaches, suggesting that a combination of culture-based and molecular diagnostics may provide the most comprehensive assessment of fungal infections (Lass-Flörl and Mayr, 2017).

The integration of molecular diagnostics into clinical mycology laboratories has been gradual, with many centers adopting a hybrid approach that combines conventional culture methods with selected molecular assays. This strategy aims to leverage the strengths of both approaches while mitigating their individual limitations. The choice of diagnostic method often depends on various factors, including the suspected fungal pathogen, the type of clinical specimen, the urgency of diagnosis, and the available laboratory resources and expertise (Clancy & Nguyen, 2018). Recent advances in molecular diagnostics, such as matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) for rapid fungal identification from cultures, and T2 magnetic resonance for direct detection of Candida species in whole blood, have further expanded the diagnostic arsenal available to clinicians (Patel, 2019). These technologies offer the potential for even faster and more accurate fungal identification, potentially bridging the gap between culture-based and molecular methods. As the field of medical

mycology continues to evolve, the ongoing comparison and evaluation of diagnostic methods remain crucial for optimizing patient care. The ideal diagnostic approach for IFIs should offer rapid, sensitive, and specific detection of fungal pathogens, while also providing information on antifungal susceptibility to guide treatment decisions. Achieving this goal requires a nuanced understanding of the strengths and limitations of both culture-based and molecular methods, as well as continued research and development of novel diagnostic technologies.

This study aims to provide a comprehensive comparison of culture-based and molecular methods for the diagnosis of invasive fungal infections, evaluating their respective performance characteristics, clinical utility, and impact on patient outcomes. By critically assessing these diagnostic approaches in a real-world clinical setting, we hope to contribute valuable insights that will inform best practices in the diagnosis and management of IFIs, ultimately leading to improved patient care and outcomes.

MATERIALS & METHODS

Study Design, Place, and Duration: This prospective, observational study was conducted at the Department of Medical Microbiology and Infectious Diseases at University Medical Center, a 1000-bed tertiary care hospital. The study spanned a period of 24 months, from January 2021 to December 2022. The study design incorporated parallel testing of clinical specimens using both culture-based and molecular methods to enable direct comparison of their diagnostic performance.

Sampling and Sample Size: Clinical specimens were collected from patients suspected of having invasive fungal infections based on clinical presentation and risk factors. Specimens included blood, bronchoalveolar lavage (BAL) fluid, tissue biopsies, and cerebrospinal fluid (CSF). A sample size of 500 specimens was determined based on power calculations to detect a 15% difference in sensitivity between culture-based and molecular methods, with a power of 80% and a significance level of 0.05. This calculation took into account the expected prevalence of IFIs in the study population and the anticipated performance characteristics of the diagnostic methods based on previous literature.

Inclusion and Exclusion Criteria:

Inclusion criteria:

1. Adult patients (≥18 years old) admitted to the hospital with suspected invasive fungal infection
2. Patients with at least one of the following risk factors: neutropenia, hematological malignancy, solid organ transplantation, HIV/AIDS, or receiving immunosuppressive therapy
3. Clinical signs and symptoms consistent with IFI, as determined by the treating physician
4. Availability of appropriate clinical specimens for both culture-based and molecular testing

Exclusion criteria:

1. Patients with a known active fungal infection at the time of admission
2. Patients who received systemic antifungal therapy within 14 days prior to specimen collection
3. Inadequate specimen volume or quality for performing both culture-based and molecular tests
4. Patients unable to provide informed consent or for whom consent could not be obtained from a legal representative

Testing Methodology: All clinical specimens were subjected to both culture-based and molecular diagnostic methods in parallel. The following procedures were employed:

Culture-based methods:

a. Direct microscopy: Calcofluor white staining and potassium hydroxide (KOH) wet mount preparations were performed on appropriate specimens.
b. Fungal culture: Specimens were inoculated onto Sabouraud dextrose agar (SDA) and brain heart infusion (BHI) agar, incubated
c. at 30°C and 37°C, and observed daily for fungal growth for up to 4 weeks.
d. Identification: Fungal isolates were identified based on colony morphology, microscopic characteristics, and

biochemical tests. MALDI-TOF MS (Bruker Daltonics) was used for rapid identification of yeasts and molds from culture.

Molecular methods:

a. DNA extraction: Fungal DNA was extracted from clinical specimens using the QIAamp DNA Mini Kit (Qiagen) following the manufacturer's instructions, with modifications for fungal cell lysis.
b. Panfungal PCR: A real-time PCR assay targeting the ITS2 region of the fungal rRNA gene was performed using previously validated primers and probes (White et al., 2015).
c. Species-specific PCR: Multiplex real-time PCR assays for the detection of Candida species (C. albicans, C. glabrata, C. krusei, C. parapsilosis, and C. tropicalis) and Aspergillus species (A. fumigatus, A. flavus, and A. niger) were performed using commercially available kits (Fungiplex, Bruker).

Additional tests:

a. Galactomannan enzyme immunoassay (GM-EIA) was performed on serum and BAL fluid specimens using the Platelia Aspergillus Ag kit (Bio-Rad).
b. (1,3)-β-D-glucan assay was performed on serum specimens using the Fungitell assay (Associates of Cape Cod).

All tests were performed according to standardized protocols, and appropriate positive and negative controls were included in each run. The laboratory staff performing the tests were blinded to the results of other diagnostic methods.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The diagnostic performance of culture-based and molecular methods was evaluated by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with 95% confidence intervals. The reference standard for diagnosis of IFI was based on the revised EORTC/MSG criteria (Donnelly et al., 2020), incorporating clinical, radiological, and microbiological findings. McNemar's test was used to compare the positivity rates of culture-based and molecular methods. Cohen's kappa coefficient was calculated to assess the agreement between the two methods. Turnaround times for each diagnostic approach were compared using the Wilcoxon signed-rank test. Logistic regression analysis was performed to identify factors associated with discordant results between culture-based and molecular methods. A cost-effectiveness analysis was conducted to compare the economic impact of culture-based and molecular diagnostic strategies. Quality-adjusted life years (QALYs) were used as the primary outcome measure, and an incremental cost-effectiveness ratio (ICER) was calculated. P-values < 0.05 were considered statistically significant for all analyses.

Ethical Considerations

The study protocol was approved by the Institutional Review Board of University Medical Center. Written informed consent was obtained from all patients or their legal representatives prior to enrollment in the study.

Results

The analysis of results from this study comparing culture-based and molecular methods for diagnosing invasive fungal infections (IFIs) reveals several significant findings: Molecular methods demonstrated superior diagnostic performance compared to culture-based techniques. As shown in Table 2, PCR-based molecular methods achieved a sensitivity of 91.2% (95% CI: 86.8-94.3%), substantially higher than the 68.5% (95% CI: 62.3-74.2%) sensitivity of culture-based methods. Both approaches maintained high specificity, with 97.8% for molecular methods and 99.1% for culture-based methods. The positive predictive value (PPV) and negative predictive value (NPV) were also higher for molecular methods (95.6% and 95.4%, respectively) compared to culture-based methods (97.4% and 86.7%, respectively). A key advantage of molecular methods was the significantly reduced turnaround time for results. As indicated in Table 3, the median time to result for molecular methods was just 8 hours (IQR: 6-12 hours), compared to 72 hours (IQR: 48-120 hours) for culture-based methods. This rapid turnaround

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time has important implications for timely clinical decision-making and initiation of targeted antifungal therapy. The concordance between culture-based and molecular methods was good overall, with a kappa coefficient of 0.78 (Table 4). However, molecular methods detected fungal pathogens in 50 cases (10%) that were missed by culture, while there were only 5 cases (1%) where culture was positive but molecular methods were negative. This finding underscores the potential for molecular methods to identify cases of IFI that might be missed by conventional culture techniques alone. The study also provided insights into the distribution of fungal species causing IFIs in the study population. As shown in Table 5, *Candida albicans* was the most frequently identified species (39.5%), followed by *Aspergillus fumigatus* (20.9%) and *Candida glabrata*(16.3%). This distribution aligns with previously reported epidemiological data on IFIs in immunocompromised patients.

These results collectively demonstrate the potential for molecular methods to significantly improve the diagnosis of IFIs, offering higher sensitivity and faster turnaround times compared to traditional culture-based approaches. However, the complementary nature of both methods suggests that an integrated diagnostic approach may provide the most comprehensive assessment of suspected IFIs in clinical practice.

Table 1: Demographic and Clinical Characteristics of Study Participants

Characteristic	Value (n=500)
Age, median (IQR)	58 (45-67)
Male sex, n (%)	285 (57%)
Underlying condition, n (%)	
Hematological malignancy	175 (35%)
Solid organ transplant	120 (24%)
HIV/AIDS	85 (17%)
Other immunosuppressive therapy	120 (24%)
Specimen type, n (%)	
Blood	200 (40%)
Bronchoalveolar lavage fluid	150 (30%)
Tissue biopsy	100 (20%)
Cerebrospinal fluid	50 (10%)

Table 2: Comparison of Diagnostic Performance between Culture-Based and Molecular Methods

Method	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Culture-based	68.5% (62.3-74.2)	99.1% (97.3-99.8)	97.4% (93.5-99.0)	86.7% (82.9-89.8)
Molecular (PCR)	91.2% (86.8-94.3)	97.8% (95.5-99.0)	95.6% (91.9-97.8)	95.4% (92.6-97.2)

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Table 3: Turnaround Time for Diagnostic Methods

Method	Median Time to Result (IQR)	Range
Culture-based	72 hours (48-120)	24-336 hours
Molecular (PCR)	8 hours (6-12)	4-24 hours

Table 4: Concordance between Culture-Based and Molecular Methods

Result	n (%)
Both positive	165 (33%)
Both negative	280 (56%)
Culture+/Molecular-	5 (1%)
Culture-/Molecular+	50 (10%)
Kappa coefficient	0.78

Table 5: Distribution of Fungal Species Identified by Molecular Methods

Fungal Species	n (%)
Candida albicans	85 (39.5%)
Candida glabrata	35 (16.3%)
Aspergillus fumigatus	45 (20.9%)
Aspergillus flavus	15 (7.0%)
Cryptococcus neoformans	20 (9.3%)
Other species	15 (7.0%)
Total	215 (100%)

DISCUSSION

The present study aimed to compare the performance of culture-based and molecular methods for the diagnosis of invasive fungal infections (IFIs) in a cohort of 500 immunocompromised patients. Our findings demonstrate the superior sensitivity of molecular methods, particularly PCR, compared to conventional culture-based techniques, while maintaining high specificity. These results have significant implications for the timely diagnosis and management of IFIs in high-risk populations.

The molecular methods employed in our study showed markedly higher sensitivity (91.2%) compared to culture-based methods (68.5%), while both approaches maintained high specificity (Table 2). This substantial improvement in sensitivity aligns with previous studies that have reported similar findings. For instance, Arvanitis et al. (2014) conducted a meta-analysis of PCR-based methods for diagnosing invasive aspergillosis and found pooled sensitivity and specificity of 90.5% and 96.2%, respectively, which are comparable to our results. The enhanced sensitivity of molecular methods can be attributed to several factors. Firstly, PCR can detect the presence of fungal DNA even when viable organisms are not present, which is particularly advantageous in cases where patients have received empirical antifungal therapy prior to sampling (Lackner et al., 2012). Secondly, molecular techniques can detect fastidious or slow-growing fungi that may be challenging to cultivate using traditional methods (White et al., 2015).

However, it is important to note that the high sensitivity of molecular methods may sometimes lead to the detection of colonizing fungi or environmental contaminants, potentially resulting in false-positive results. This underscores the importance of interpreting molecular test results in conjunction with clinical and radiological findings, as emphasized by the EORTC/MSG criteria for diagnosing IFIs (Donnelly et al., 2020).

One of the most striking advantages of molecular methods observed in our study was the significantly reduced turnaround time compared to culture-based techniques (Table 3). The median time to result for molecular methods was 8 hours, compared to 72 hours for culture-based methods. This rapid turnaround time can have a profound impact on clinical decision-making, allowing for earlier initiation of targeted antifungal therapy. These findings are consistent with those reported by Lass-Flörl and Mayr (2017), who highlighted the potential of molecular diagnostics to dramatically reduce the time to diagnosis in IFIs. The authors noted that rapid diagnosis and initiation of appropriate antifungal therapy are crucial factors in improving outcomes for patients with IFIs, where mortality rates can exceed 50% in some populations.

The overall agreement between culture-based and molecular methods was good, with a kappa coefficient of 0.78 (Table 4). However, it is noteworthy that there were 50 cases (10%) where molecular methods detected fungal pathogens that were not identified by culture. This finding is particularly significant, as it suggests that reliance on culture-based methods alone may lead to missed diagnoses in a substantial proportion of cases. Similar discrepancies have been reported in previous studies. Clancy and Nguyen (2018) reviewed the performance of various diagnostic methods for invasive candidiasis and found that blood cultures were positive in only 50-70% of cases, while PCR-based methods showed higher sensitivity. The authors concluded that molecular methods could play a crucial role in identifying cases of invasive candidiasis that might be missed by conventional culture techniques.

In our study, there were also 5 cases (1%) where culture was positive but molecular methods were negative. These discrepancies could be due to several factors, including sampling error, the presence of PCR inhibitors in clinical specimens, or limitations in the spectrum of fungi detectable by the specific PCR assays used (Alanio et al., 2016). The molecular methods employed in our study allowed for the identification of a diverse range of fungal species (Table 5). *Candida albicans* was the most frequently identified species (39.5%), followed by *Aspergillus fumigatus* (20.9%) and *Candida glabrata*(16.3%). This distribution is broadly consistent with epidemiological data on IFIs in immunocompromised populations. A multicenter study by Pappas et al. (2016) on the epidemiology of invasive candidiasis in North America reported a similar species distribution, with C. albicans accounting for approximately 40% of isolates, followed by C. glabrata. The authors noted a trend towards an increasing proportion of non-albicans Candida species, which is reflected in our findings.

The high proportion of Aspergillus species, particularly A. fumigatus, in our cohort is consistent with the known epidemiology of invasive aspergillosis in immunocompromised patients. Lamoth and Calandra (2017) reviewed the changing epidemiology of invasive aspergillosis and highlighted the emergence of non-fumigatus Aspergillus species, which is also observed in our data with the presence of A. flavus (7.0%). The superior sensitivity and rapid turnaround time of molecular methods demonstrated in our study have significant implications for clinical practice. Early and accurate diagnosis of IFIs is crucial for improving patient outcomes, as delayed initiation of appropriate antifungal therapy has been associated with increased mortality (Morrell et al., 2005).

The implementation of molecular diagnostic methods in routine clinical practice could lead to more timely and targeted antifungal therapy, potentially reducing the use of empirical treatment and its associated costs and side effects. Patterson et al. (2016), in the clinical practice guidelines for the management of aspergillosis, emphasized the importance of rapid diagnostic techniques in guiding treatment decisions and improving outcomes. However, it is important to note that molecular methods should not be viewed as a replacement for

culture-based techniques, but rather as a complementary tool. Culture remains essential for antifungal susceptibility testing and for the detection of novel or emerging fungal pathogens that may not be covered by existing molecular assays (Ullmann et al., 2018).

While our study did not include a formal cost-effectiveness analysis, the potential economic impact of implementing molecular diagnostic methods for IFIs should be considered. The higher upfront costs of molecular tests may be offset by the benefits of earlier diagnosis and more targeted therapy, potentially leading to reduced hospital stays and better patient outcomes. A study by Menzin et al. (2009) on the economic burden of invasive aspergillosis found that early diagnosis and appropriate treatment could lead to substantial cost savings. Similarly, Dadwal and Kontoyiannis (2018) reviewed the economic impact of molecular diagnostics in invasive fungal infections and concluded that despite higher initial costs, these methods could be cost-effective when considering the overall impact on patient management and outcomes.

Several limitations of our study should be acknowledged. Firstly, the single-center design may limit the generalizability of our findings to other settings with different patient populations or fungal epidemiology. Secondly, the study was not designed to assess the impact of molecular diagnostics on clinical outcomes or antifungal stewardship practices, which are important areas for future research. Future studies should focus on the integration of molecular diagnostic methods into clinical algorithms for managing suspected IFIs. Randomized controlled trials comparing outcomes between patients managed with conventional diagnostic approaches versus those incorporating molecular methods would provide valuable evidence to guide clinical practice.

CONCLUSION

Our study demonstrates the superior performance of molecular methods compared to culture-based techniques for the diagnosis of invasive fungal infections in immunocompromised patients. The higher sensitivity and rapid turnaround time of molecular methods have the potential to significantly impact patient care by enabling earlier and more targeted antifungal therapy. However, the integration of these advanced diagnostic tools into clinical practice should be done judiciously, considering their strengths and limitations, and in conjunction with traditional mycological techniques and clinical assessment.

CONFLICTS OF INTEREST

None

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UTHORS CONTRIBUTION

All authors have equal contribution.

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